UNITED STATES DEPARTMENT OF COMMERCE
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VB

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/381,497	02/17/00	FITZGERALD D	015280-31710

HM22/1102

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	10

DATE MAILED: 11/02/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/381,497	Applicant(s) FitzGerald et al
	Examiner Larry R. Helms Ph.D.	Group Art Unit 1642

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-39* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-39* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 1-39 are under examination.

Claim Objections

2. Claim 37 is objected to because of the following informalities: The claim recites a VL of SEQ ID NO:2, SEQ ID NO:2 is a VH. The claim should recite a VL of SEQ ID NO:4. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-10, 12, 15-16, 18-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1, 7, 8, 29, and 30 and those dependent on these claims are indefinite for reciting "bonded" because the exact meaning of the term is not clear. Does the term mean covalently attached or non-covalently attached?

b. Claim 5, 12, and 27 are indefinite for reciting the term "RFB4" because other laboratories/inventors may use the same laboratory designation to refer to different antibodies.

Amendment of the claim to insert the corresponding ATCC accession number of the hybridoma which produces the antibody or to add the SEQ ID Nos of the heavy and light chain variable regions would overcome this rejection.

c. Claims 6, 15, 18-21, 33, and 37 are indefinite for reciting the phrase "substantially similar" because the exact meaning of the phrase is not clear. The specification defines the phrase as "a sequence with at least 90%, preferably at least 95% sequence identity to the reference sequence" (see page 12, lines 19-21). However, it remains unclear what sort of alignment is allowed (i.e., gaps, mismatches) and which amino acid residues are considered to be similar. Further, despite the high level of skill in the genetic analysis art, there remains a lack of development concerning the definition of the phrase "substantially similar. One cannot therefore determine what is meant by the phrase "substantially similar".

d. Claim 12 is indefinite because it contains the abbreviation "dsFv". Full terminology should be in first instance of the claims followed by the abbreviation in parentheses. Dependent claims may then use the abbreviation. Abbreviations render the claim indefinite because the same abbreviation may represent more than one element or concept.

e. Claims 22-32 are indefinite for reciting incomplete method claims which do not clearly set forth method steps and does not include a resolution step which reads back on the preamble of the claimed method. Merely contacting a malignant B-cell with an antibody does not result in a method of inhibiting the growth of a malignant B-cell. The claims should conclude with a step inhibiting the growth of the malignant B-cell, for example, thereby as

required by the preamble, which recites "a method for inhibiting the growth of a malignant B-cell".

f. Claim 34 recites the limitation "the anti-CD22 Fv fragment" in claim 33. There is insufficient antecedent basis for this limitation in claim 33.

g. Claims 5 and 27 are indefinite for reciting "RFB4 binding fragment" because the exact meaning of the phrase is not clear. Does the phrase mean the antibody binds to RFB4?

h. Claims 1-17 and 22-32 are indefinite for reciting amino acid position "44' and "100" in claims 1 and 11 because the exact meaning of the terms are not clear. Is the numbering system according to Kabat, Chothia, or some other system?

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 6, 8-10, 15-21, 28, and 33-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses SEQ ID Nos 1-4, however, the sequence listing lists SEQ ID Nos 1-4 different than that disclosed in the specification. SEQ ID NO:2 in the sequence listing contains a lysine residue at position 61 in the light chain, however, the specification in Figure 1

discloses an arginine at this position. SEQ ID NO:4 in the sequence listing contains a valine at position 121, however, the specification in Figure 1 discloses a threonine at position 121. Likewise, the nucleic acid sequence of SEQ ID Nos 1 and 3 are not as disclosed in Figure 1. The response of 5/15/00 does not state where support for these changes are in the specification of the claims as originally filed. Applicant is required to either point to where the specification provides support for the phrase or to remove it from the claims.

7. Claims 1-5, 7-14, 17-19, 22-24, 26-27, 29-32, and 39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunoconjugate comprising a toxin of PE or PE38 or a detectable label peptide linked to a recombinant anti-CD22 antibody of RFB4 with a VL of SEQ ID NO:4 which contains a cysteine at amino acid position 100 and a VH of SEQ ID NO:2 with a cysteine at position 44, wherein the VH chain is covalently attached to the amino terminus of PE or PE38 and the VL and VH are linked through a liner peptide of SEQ ID NO:5 or through a cysteine-cysteine disulfide bond, an expression cassette encoding said immunoconjugate, a host cell, a method of inhibiting the growth of a rodent, canine, or primate malignant B-cell, does not reasonably provide enablement for a recombinant immunoconjugate comprising PE or PE38 or a detectable label peptide linked to any recombinant anti-CD22 antibody with any VH having a cysteine at position 44 and any VL with a cysteine at position 100 which does not bind antigen, or expression cassettes comprising such, or a VH sequence of SEQ ID NO:2 or a VL sequence of SEQ ID NO:4 which separately would

not bind antigen, or a method of inhibiting the growth of any malignant B-cell with a conjugate with a detectable label for inhibiting the growth of any malignant B-cell or a method of inhibiting the growth of malignant B-cells in vivo in humans or detecting the presence of CD22 in vivo in a mammal including a human. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to any anti-CD22 antibody with a cysteine at position 44 of the VL and position 100 in the VL and immunoconjugates comprising such that do not have to bind antigen and an anti-CD22 antibody which contains any VH with the cysteine at position 44 and any VL with a cysteine at position 100, a VH sequence of SEQ ID NO:2 and a VL sequence of SEQ ID NO:4, a method of inhibiting the growth of any malignant B-cell with a detectable label antibody including human malignant B-cells and detection of CD22 in vivo in a mammal including a human.

The specification teaches the RFB4 antibody which comprises a cysteine at position 44 in the VH and a cysteine at position 100 in the VL covalently coupled to PE (PE38). The specification teaches a method of inhibiting the growth of CA46 tumor cells in mice and primates and in CD22 positive cells from human patients (in vitro) with the RFB4(dsFv)-PE38 construct. The specification fails to enable any other anti-CD22 antibody comprising a cysteine at position 44 in the VH and a cysteine at position 100 in the VL except the RFB4 antibody. The specification fails to enable a VH or a VL separately that would function in antigen binding. The specification fails to enable a detectably labeled antibody that would inhibit the growth of malignant B-cells, or a method of inhibiting human malignant B-cells in vivo or detecting in vivo in a mammal which includes humans.

The claims are broadly drawn to a VH of SEQ ID NO:2 and a VL of SEQ ID NO:4 that separately would not bind antigen, any anti-CD22 antibody with any VH with a cysteine at position 44 and any Vl with a cysteine at position 100 which does not have to bind antigen. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences

which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that a VH or a VL or an antibody that may contain any VH pared with any VL as defined by the claims, have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity. In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986).

Claim 22 is broadly drawn to a method of inhibiting the growth of a malignant B-cell with an anti-CD22 antibody and a detectable label, however, the specification does not teach inhibition of any malignant B-cell with such a conjugate. Moreover, the method is broadly drawn to a method of inhibiting malignant B-cells in humans in vivo wherein the specification only teaches a method in mice. Chatterjee et al state the art recognized experience that for any

novel therapy, the transition for the laboratory to the clinic (animal experiments to the bedside) is a quantum leap (Cancer Immunol. Imunother., 1994, see Introduction). Results obtained under controlled conditions and in inbred animals, as in the instant specification where mice are used as a test animal, often differ from the clinical response obtained in patients. This applies to strategies drawn to cancer therapy.

Claim 39 encompasses detection of Cd22 in vivo in a human. The specification has not adequately taught how one skilled in the art would be able to specifically detect the target with the disclosed antibodies in vivo in a human. As indicated in US Patent 4,722,899 (Hamaoka et al), "the reagent used for immunoassay (antibody) is believed to be highly specific to the substance to be assayed (antigen), the assay specificity tends to be affected by the crossreactive substances which are structurally related to the substances to be assayed" (see column 1, lines 28-36). Although monoclonal antibodies are highly specific, the antibodies do possess a certain degree of cross reactivity (see column 4, lines 53-56 of US Patent 4,474,893 (Reading, C.L.)). Further, Sevier et al (Clin Chem 1981; Vol 27 No 11:1797-1806) teach that if an antibody binds to a common subunit, the antibody is not useful in a selective detection procedure (see page 1798, right column). Besides the target of interest, there may be other structurally related substances present in the sample. Therefore, without actually testing the sample, it is doubtful that the claimed monoclonal antibody would detect the target per se accurately in the sample.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

8. Claims 5, 12, and 27 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line which produces an antibody having the exact chemical identity of RFB4 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

a. For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The

results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species RFB4. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Priority

9. Claims 6, 15, 18-21, 28, 33, and 37 recite the limitations of SEQ ID Nos 1-4. The limitation of these SEQ ID Nos are not found in the provisional application 60/041437, filed 3/20/97 (see also 112 first paragraph, new matter rejection above). As such claims 6, 8-10, 15-21, 28, and 33-39 are granted the priority date of the filing date of the instant application, 2/17/00.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 6, 8-10, 15-21, 28, and 33-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Fitzgerald et al (WO 98/41641, published 9/24/98).

a. The claims recite a recombinant immunotoxin, comprising a therapeutic agent or a detectable label peptide bonded to a recombinant anti-CD22 antibody having a VH with a cysteine at amino acid position 44 and a VL with a cysteine at amino acid position 100 wherein the VH is substantially similar to SEQ ID NO:2 and the VL is substantially similar to SEQ IS NO:4, wherein the VH and VL are bonded through a peptide linker SEQ ID NO:5 or a cysteine-cysteine disulfide bond, an expression cassette, a host cell with the expression cassette, a VH of SEQ ID NO:2, a VL of SEQ ID NO:4, a nucleic acid of SEQ ID NO:1 and 3, a method of inhibiting the growth of malignant B-cells with an immunoconjugate comprising SEQ ID NO:2 and SEQ ID NO:4, an anti-CD22 antibody comprising SEQ ID NO:2 and 4 detectably labeled or conjugated to PE or a cytotoxic fragment thereof, a method of detecting the presence of CD22 in a mammal.

b. Fitzgerald et al teach a recombinant immunotoxin, comprising a therapeutic agent or a detectable label peptide bonded to a recombinant anti-CD22 antibody having a VH with a cysteine at amino acid position 44 and a VL with a cysteine at amino acid position 100 wherein the VH is substantially similar to SEQ ID NO:2 and the VL is substantially similar to SEQ IS NO:4, wherein the VH and VL are bonded through a peptide linker SEQ ID NO:5 or a cysteine-cysteine disulfide bond, an expression cassette, a host cell with the expression cassette, a VH of SEQ ID NO:2, a VL of SEQ ID NO:4, a nucleic acid of SEQ ID NO:1 and 3, a method of

inhibiting the growth of malignant B-cells with an immunoconjugate comprising SEQ ID NO:2 and SEQ ID NO:4, an anti-CD22 antibody comprising SEQ ID NO:2 and 4 detectably labeled or conjugated to PE or a cytotoxic fragment thereof, a method of detecting the presence of CD22 in a mammal (see entire document).

12. Claim 19 is rejected under 35 U.S.C. 102(b) as being anticipated by Rodriguez et al (WO 95/30004, published 11/9/95).

a. The claim recites a VL sequence substantially similar to that of SEQ ID NO:4.

b. Rodriguez et al teach an amino acid sequence (SEQ ID NO:1) that is 97% identical to SEQ ID NO:4 (see attached sequence alignment attached to the back of this Office Action, "Db" is the sequence of Rodriguez et al and "Qy" is SEQ ID NO:4 of the instant application).

13. Claims 6, 8, 10, 18, 19, 28, 33, 35-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Kreitman et al (Proc. Of the American Association for Cancer Res. 38:28, 1997).

a. The claims have been described supra.

b. Kreitman et al teach RFB4(dsFv)-PE38 and a method of inhibiting the growth of malignant B-cells with the antibody conjugate.

Kreitman et al is silent about the SEQ ID NOs of the VH and the VL, however, it is the Examiner's position that Kreitman et al have produced an antibody that is directed to the same antigen CD22 as recited in the claims and that the antibody is named RFB4 and this antibody has

the same properties and amino acid sequence of the VH and VL as that claimed. One of ordinary skill in the art would reasonably conclude that Kreitman et al's antibody also possesses the same binding to the CD22 protein and same structural and physical properties, therefore, it appears that Kreitman et al have produced an antibody that is identical to the claimed antibody RFB4 which has the same VH and VL as claimed and can be used to assay the same CD22 protein. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed antibody RFB4 or the claimed antigen CD22 with the antibody and the CD22 antigen of Kreitman et al, the burden of proof is upon the Applicants to show a distinction between the structural, sequence, and functional characteristics of the claimed antibody and the antigen and the antibody and the antigen of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

14. Claims 33 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Ghetie et al (Cancer Res. 51:5876-5880, 1991).

a. The claims recite an anti-CD22 antibody comprising a VH of SEQ ID NO:2 and a VL of SEQ ID NO:4 conjugated to a therapeutic agent.

b. Ghetie et al teach the RFB4 antibody which is an anti-CD22 antibody conjugated to ricin A.

Ghetie et al is silent about the SEQ ID NOs of the VH and the VL, however, it is the Examiner's position that Ghetie et al have produced an antibody that is directed to the same antigen CD22 as recited in the claims and that the antibody is named RFB4 and this antibody has the same properties and amino acid sequence of the VH and VL as that claimed. One of ordinary skill in the art would reasonably conclude that Ghetie et al's antibody also possesses the same binding to the CD22 protein and same structural and physical properties, therefore, it appears that Ghetie et al have produced an antibody that is identical to the claimed antibody RFB4 which has the same VH and VL as claimed and can be used to assay the same CD22 protein. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed antibody RFB4 or the claimed antigen CD22 with the antibody and the CD22 antigen of Kreitman et al, the burden of proof is upon the Applicants to show a distinction between the structural, sequence, and functional characteristics of the claimed antibody and the antigen and the antibody and the antigen of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ghetie et al (Cancer Res. 51:5876-5880, 1991) and further in view of Reiter et al (Biochemistry 33:5451-5459, 1994) and Kuan et al (Biochemistry 35:2872-2877, 1996, Abstract published 2/1/96).

a. The claims recite an anti-CD22 antibody of RFB4 comprising a PE and a VH with a cysteine at position 44 and a VL with a cysteine at position 100 wherein the VH is SEQ ID NO:2 and the VL is SEQ ID NO:4, wherein the VH is bonded to the amino terminus of PE and the VH and VL are bonded through a linker of SEQ ID NO:5 or cysteine-cysteine disulfide bond, an expression cassette comprising such, a host cell, a method of inhibiting the growth of malignant B-cells in a rodent.

b. Ghetie et al teach the RFB4 anti-CD22 antibody conjugated to ricin A chain and inhibition of growth of B-cell lymphomas in mice. Ghetie et al does not teach an anti-CD22 antibody with a VH with a cysteine at position 44 or a VL with a cysteine at position 100 conjugated to a cytotoxic fragment of PE wherein the VH is linked to the PE at the amino terminus, and the VH and VL are linked through a peptide linker that has SEQ ID NO:5 or a disulfide bond, or an expression cassette comprising such or a method of inhibiting the growth of malignant B-cells with a anti-CD22 antibody PE conjugate. These deficiencies are made up for in the teachings of Kuan et al and Reiter et al.

c. Reiter et al teach recombinant immunotoxins comprising disulfide stabilization with a cysteine at position 44 in the VH and a cysteine at position 100 in the VL. The antibody is conjugated to a toxin of PE38. Reiter et al also teach the VH is linked to the amino terminus of PE38 (see Figure 2). Reiter et al teach a general method for producing disulfide stabilized immunotoxins (see page 5453, Results). p5453

d. Kuan et al teach a disulfide stabilized Fv directed to a cancer antigen. Kuan et al teach the VH is linked to the amino terminus of PE38 nd the VH and VL are linked through a sequence that has SEQ ID NO:5 and the VH and VL are linked through a disulfide bond and expression cassettes and host cells comprising such.

e. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the antibody RFB4 and the method of inhibiting malignant B-cells as taught by Ghetie et al and use the method of Reiter et al and Kuan et al to produce a disulfide stabilized anti-CD22 antibody conjugate.

f. One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody RFB4 and the method of inhibiting malignant B-cells as taught by Ghetie et al and use the method of Reiter et al and Kuan et al to produce a disulfide stabilized anti-CD22 antibody conjugate because Ghetie et al teach that the RFB4 conjugates inhibited protein synthesis and when administered to mice with tumors, extended the mean survival time (see abstract). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody RFB4 and the method of inhibiting malignant B-cells as taught by Ghetie et al and use the method of Reiter et al and Kuan et al to produce a disulfide stabilized anti-CD22 antibody conjugate because Reiter et al teach a general method of stabilizing Fv's with insertion of cysteine residues in the conserved framework residues (see page 5453, Results) and "Neither molecular modeling nor knowledge of the structures of these Fv's was necessary to identify these positions" (see page

5453) and "disulfide-stabilized Fv's could be used not only to generate immunotoxins but also for all of the diagnostic and therapeutic uses proposed for single-chain antibodies or antigen binding proteins" (see page 5458). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody RFB4 and the method of inhibiting malignant B-cells as taught by Ghetie et al and use the method of Reiter et al and Kuan et al to produce a disulfide stabilized anti-CD22 antibody conjugate because Kuan et al teach immunotoxins comprising a disulfide stabilized VH and VL wherein the VH is linked to the amino terminus of the PE38 and "We have compared the stability of three different single-chain and dsFv inmmunotoxins, and in all three cases the dsFv immunotoxins were more stable (see page 2872). Moreover, it would have been obvious to one of skilled in the art at the time the claimed invention was made to use a linker which has SEQ ID NO:5 to link the VH and the VL domains as was commonly performed.

g. Although the references do not teach the amino acid sequences of SEQ ID NO:2 and 4 for the VH and VL of the anti-CD22 RFB4 antibody, it would be obvious that the antibody of Ghetie et al would have the sequence of the VH of SEQ ID NO:2 and a VL of SEQ ID NO:4.

h. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

17. Claims 37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kreitman et al (Cancer Res. 53:819-825, 1993) and further in view of Ghetie et al (Cancer Res. 51:5876-80, 1991).

a. The claims have been described supra. Claim 37 is being interpreted as reciting a VL substantially similar to SEQ ID NO:4.

b. Kreitman et al teach a method of detecting CD22 in a biological sample with an anti-CD22 antibody that is detectably labeled (see page 820, Binding studies). Kreitman et al does not teach an antibody that comprises a VH and VL of SEQ ID NO:2 and 4. This deficiency is made up for in the teachings of Ghetie et al.

c. Ghetie et al has been described supra.

d. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the antibody RFB4 of Ghetie et in the method of detection as taught by Kreitman et al.

e. One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody RFB4 as taught by Ghetie et al in the method of Kreitman et al because Kreitman et al teach an assay of an anti-CD22 antibody to CD22 antigen in order to determine whether the conjugates were specific for the antigen (see page 821, cytotoxic specificity). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody RFB4 as taught by Ghetie et al in the method of Kreitman et al because Ghetie et al teach an anti-CD22 antibody, RFB4,

which binds to CD22 and Ghetie et al teach a toxin conjugate and it would have been obvious for Ghetie et al to use the method of Kreitman et al to determine whether the RFB4 conjugate antibody is specific for the binding to cells using an RFB4 antibody with a detectable label.

f. Although the references do not teach the amino acid sequences of SEQ ID NO:2 and 4 for the VH and VL of the anti-CD22 RFB4 antibody, it would be obvious that the antibody of Ghetie et al would have the sequence of the VH of SEQ ID NO:2 and a VL of SEQ ID NO:4.

g. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusions

18. No Claims are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a

general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

20. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

Sheela Huff

SHEELA HUFF
PRIMARY EXAMINER